

Application No.: 10/001945

Docket No.: PPI-106CP2

REMARKS

Claims 1-65 were pending in the application. Claims 20-56 and 58-61 have been cancelled without prejudice, claims 1-6, 19, 57, and 62 have been amended and new claims 69-71¹ have been added. Accordingly, after the amendments presented herein have been entered, claims 1-19, 57, 62-65 and 69-71 will remain pending.

This paper addresses the issues raised in the Final Office Action, dated July 29, 2005, and the Advisory Action, dated October 20, 2005.

No new matter has been added by the foregoing claim amendments. Support for the amendments to the claims may be found throughout the specification and claims as originally filed. Specifically, the amendments to claims 2-6 were made to provide proper dependencies. Support for the amendments to claim 1 can be found, for example, at page 15, lines 15-17 of the specification as originally filed. Applicants have designated the formula $-NR_2R_3$ as $-NR_2R_3$ in the claim to avoid any confusion with the first occurrence of R_2 and R_3 in the claim, consistent with the Examiner's suggestion. Support for the amendments to claim 19 can be found, for example, in original claim 19, and at page 8, line 10 of the specification as originally filed. Support for the amendments to claim 57 can be found, for example, throughout the Examples at page 43, line 23 through page 59, line 2 of the specification as originally filed. Support for the amendments to claim 62 can be found, for example, at least at page 7, lines 5-11 and at page 15, lines 15-18 of the specification as originally filed. New claims 69-71 correspond to claims 2-4. Support for new claim 69 can be found, for example, at least in original claim 2 and at page 3, lines 14-16 of the specification as originally filed. Support for new claim 70 can be found, for example, at least in original claim 3, and at page 3, lines 14-16 of the specification as originally filed. Support for new claim 71 can be found, for example, at least in original claim 4, and at page 3, lines 14-16 of the specification as originally filed.

Support for the amendments to the specification at page 15, lines 3-13, page 61, Table IV and page 61-62, Table V, can be found, for example, in the Examples section at page 43, line 23 through page 59, line 2 of the specification as originally filed.

¹ Please note that claims 66-68 presented in the Amendment and Response of September 28, 2005 were not entered. Pursuant to the Examiner's request, these claims are presented herein as claims 69-71.

Application No.: 10/001945

Docket No.: PPI-106CP2

Without acquiescing to the accuracy of the Examiner's characterization of the claims at paragraphs 14, 17, and 19 of the Final Office Action, Applicants respectfully submit that the inventions described in U.S. Patent 6,548,477, U.S. Patent 6,919,307, U.S. patent application Serial No. 09/972,772 and the present application were commonly owned at the time the invention in this application was made, as evidenced by copies of the assignments submitted on September 28, 2005 as Appendices A-D, respectively.

Cancellation of and/or amendments to the claims as should in no way be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, and were made solely in the interest of expediting prosecution of the above-identified application. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in one or more patent applications.

Cancellation of Non-Elected Species

At paragraph 1 of the Final Office Action, the Examiner has required cancellation of the non-elected amino acid sequences in claims 47 and 56.

The requirement for cancellation of the non-elected amino acid species has been rendered moot in view of the cancellation of the claims.

Objection to the Priority Claim

At paragraph 3 of the Final Office Action, the Examiner has objected to the priority claim presented in the amendment filed on June 20, 2005. Specifically, the Examiner states that "the application serial number and filing date for grandparent application 09/704,251 needs to be re-inserted so that standard priority claim language is used."

Applicants respectfully submit that the aforementioned objection to the priority claim has been rendered moot in view of the amendments to the specification presented herewith. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this objection.

Application No.: 10/001945

Docket No.: PPI-106CP2

Objections to the Disclosure

At paragraph 4 of the Final Office Action, the Examiner has objected to the disclosure. In particular, the Examiner states that

the sequence designated "SEQ ID NO:30" does not correspond to SEQ ID 30 as defined in the sequence listing filed June 17, 2003. In amended paragraph at page 15, lines 3-13, second to last line of paragraph, 'pyridylpropionic is misspelled. In Table IV at page 61, the amended amino acid sequence given for Example 14/ID#30 does not correspond the structural formula given for Example 14 at page 51.

Applicants have amended the specification in order to correct these informalities, as requested by the Examiner. In addition, on September 28, 2005, Applicants submitted a substitute computer readable form (CFR) copy of the Sequence Listing, a substitute paper copy of the Sequence Listing as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter as required by 37 CFR § 1.825(a) and (b). Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this objection to the disclosure.

Rejection of Claims 41 and 48-57 Under 35 U.S.C. §112, First Paragraph

At paragraph 5 of the Final Office Action, the Examiner has rejected claims 41 and 48-57 under 35 U.S.C. §112, first paragraph as "failing to comply with the written description requirement." In particular, the Examiner states that

[c]laims 41 and 48 have been amended so that the oxiranyl group is no longer methyl substituted. There is no original disclosure of a MetAP-2 inhibitory core having this particular structure. There is no original disclosure of the compound recited at claim 57, page 16, lines 15-16. It appears that this compound may have been intended to be a corrected version of the originally-filed compound which included "ID#40" in its name. However, there never was a SEQ ID NO:40 in any sequence listing in the application and in corresponding Example 16, there is no Asp residue. There is no original disclosure of the compound recited at claim 57, page 17, lines 1-2. The peptide portion of this compound, Ac-ProLeuMetTrpAla, is not disclosed in the sequence listing or in any of the tables or examples of the specification. There is no original disclosure of the compound recited at claim 57, page 17, lines 3-4. The peptide portion of this compound, Ac-ProLeuGlyMet, is not disclosed in the sequence listing or in any of the tables or examples of the specification.

Application No.: 10/001945

Docket No.: PPI-106CP2

Applicants respectfully submit that the aforementioned rejection of the claims has been rendered moot in view of the cancellations/amendments to the claims and the substitute Sequence Listing submitted herewith. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection of the claims.

Rejection of Claims 1-47 Under 35 U.S.C. §112, Second Paragraph

At paragraph 6 of the Final Office Action, the Examiner has rejected claims 1-47 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention". In particular, the Examiner states that

[a]t claim 1, in formula I and at lines 6 and 9-12, and in the last two lines, the same variable names R_2 and R_3 are used to designate different substituents of the compound and are defined differently from one another....For analogous reasons, independent claim 20 and dependent claims 34-41 are also indefinite...The claims should be re-written so that different variable names are used for the differently-defined substituents.

Applicants submit that the aforementioned rejection of the claims has been rendered moot in view of the cancellations/amendments to the claims presented herein. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection of the claims.

Objections to Claims 23, 24, 28, 29, 49, 50, and 57

At paragraph 7 of the Final Office Action, the Examiner has objected to claims 23, 24, 28, 29, 49, 50, and 57. Specifically, the Examiner states that

[t]he provided clauses inserted into claim 23 and 28 appear to be redundant because the claims do not permit Q to be hydrogen under any circumstances...The provided clause inserted into claim 49 appears to be redundant because the claim does not permit P to be hydrogen, NHR or OR under any circumstances...At claim 57, page 16, lines 9-16 and 19-20, and page 17, lines 1-6, SEQ ID NOS corresponding to the recited amino acid sequences must be inserted after each of the compound names...At claim 57, page 16, line 19 "Carbamoyl" is misspelled.

Applicants submit that the aforementioned objections to the claims have been rendered moot in view of the cancellations/amendments to the claims presented herein. Accordingly,

Application No.: 10/001945

Docket No.: PPI-106CP2

Applicants respectfully request that the Examiner reconsider and withdraw these objections to the claims.

Objection to Claims 2-6 and 41

At paragraph 8 of the Final Office Action, the Examiner has objected to claims 2-6 and 41 as "being of improper dependent form for failing to further limit the subject matter of the previous claim." Specifically, the Examiner states that

[i]ndependent claim 1 has been amended so that R_3 and R_4 , if they are alkyl or aryl groups, are required to be substituted alkyl or substituted aryl groups. However, dependent claims 2-6 still permit R_3 and R_4 to be unsubstituted alkyl groups, unsubstituted aryl groups, or phenyl, naphthyl, benzyl or naphthylmethyl groups... Claim 41 has been amended so that the oxiranyl group is no longer methyl-substituted. Accordingly, the A group of claim 41 is no longer a species of one of the A groups set forth in claim 40...

Applicants respectfully submit that the aforementioned objections to the claims have been rendered moot in view of the cancellations/amendments to the claims presented herein. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objections to claims.

With respect in particular to claim 4, the Examiner has indicated in the Advisory Action of October 20, 2005 that the objection to claim 4 would be maintained because "[d]ependent claim 4 does not require its alkyl groups to be substituted, as required by independent claim 1." Applicants submit that claim 4 is dependent from claim 3 which is directed to the compounds of claim 1 in which "at least one of R_3 and R_4 is a *substituted* normal, branched or cyclic C_1 - C_6 alkyl group." Therefore, it follows that the normal or branched C_1 - C_4 alkyl group presented in claim 4 as substituents for R_3 and R_4 are substituted. Nonetheless, in order to expedite allowance of the pending claims, Applicants have amended claim 4 to specify that R_3 and R_4 are substituted. In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the objection to claim 4.

Application No.: 10/001945

Docket No.: PPI-106CP2

Rejection of Claims 23, 24, and 58-61 Under the Statutory Type (35 U.S.C. §101) Double Patenting

At paragraph 10 of the Final Office Action, the Examiner has rejected claims 23, 24, and 58-61 under 35 U.S.C. §101 as "claiming the same invention as that of claims 4, 5, 9, 10, 30, 31, and 39-42 of prior U.S. Patent No. 6,548,477 [hereinafter the "'477 patent']".

Without acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting examination, Applicants have cancelled claims 23, 24 and 58-61. Accordingly, the aforementioned rejection of the claims has been rendered moot and the Examiner is respectfully requested to reconsider and withdraw this rejection.

Provisional Rejection of Claims 21-24 and 58-61 Under the Statutory Type (35 U.S.C. §101) Double Patenting

At paragraph 11 of the Final Office Action, the Examiner has provisionally rejected claims 21-24 and 58-61 under 35 U.S.C. §101 as "claiming the same invention as that of claims 21-24 and 58-61 of co-pending Application No. 10/429,174."

Without acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting examination, Applicants have cancelled claims 21-24 and 58-61. Accordingly, the aforementioned rejection of the claims has been rendered moot and the Examiner is respectfully requested to reconsider and withdraw this rejection.

Rejection of Claims 2-6, 20-22, 25-40, 42-47, and 62-65 Under the Doctrine of Obviousness-Type Double Patenting

At paragraph 13 of the Final Office Action, the Examiner has rejected claims 2-6, 20-22, 25-40, 42-47, and 62-65 under the judicially created doctrine of obvious type double patenting as "being unpatentable over claims 1-52 of U.S. Patent No. 6, 548,477." In particular, the Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '477 patent anticipate the instant claims." Furthermore, the Examiner has indicated in the Advisory Action of October 20, 2005 that

Application No.: 10/001945

Docket No.: PPI-106CP2

had Applicants' proposed response [to the Final Office Action] been entered, ***claims 2-6 and 62-65 would no longer be included in the rejection***, and claims 41, 48 and 51-56 would have to be included in the list of rejected claims due to the proposed changes to the claimed structural formulas.

Without acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting examination, Applicants have cancelled claims 20-56. Accordingly, the aforementioned rejection of the claims has been rendered moot and the Examiner is respectfully requested to reconsider and withdraw this rejection.

Provisional Rejection of Claims 1-40, 42-47, and 57-65 Under the Doctrine of Obviousness-Type Double Patenting

At paragraph 15 of the Final Office Action, the Examiner has provisionally rejected claims 1-40, 42-47, and 57-65 under the judicially created doctrine of obviousness-type double patenting as "being unpatentable over claims 1-73 of co-pending Application No.10/429,174." The Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '174 application anticipate the instant claims."

Applicants respectfully submit that, while in no way admitting that the present claims are the same or obvious over claims 1-73 of co-pending Application No. 10/429,174, the claims of co-pending Application No. 10/429,174 have been amended (see Amendment and Response dated October 7, 2005), thereby rendering this rejection moot. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw this provisional rejection of the claims.

Provisional Rejection of Claims 2-6, 20-40, 42-47, and 58-65 Under the Doctrine of Obviousness-Type Double Patenting

At paragraph 16 of the Final Office Action, the Examiner has provisionally rejected claims 2-6, 20-40, 42-47, and 58-65 under the judicially created doctrine of obviousness-type double patenting as "being unpatentable over claims 1-43, 45-48, and 50-61 of co-pending Application No.09/972,772." The Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims of

Application No.: 10/001945

Docket No.: PPI-106CP2

the '772 application anticipate the instant claims." Furthermore, the Examiner has indicated in the Advisory Action of October 20, 2005 that

had Applicants' proposed response [to the Final Office Action] been entered, *claims 2-6, 57 and 62-65 would no longer be included in the rejection*, and claims 41, 48 and 51-56 would have to be included in the list of rejected claims due to the proposed changes to the claimed structural formulas.

Without acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting examination, Applicants have cancelled claims 20-56 and 58-61. Accordingly, the aforementioned rejection of the claims has been rendered moot and the Examiner is respectfully requested to reconsider and withdraw this rejection.

Rejection of Claims 2-6, 20-40, 42-47, 57, 58, 61, 62, and 65 Under the Doctrine of Obviousness-Type Double Patenting

At paragraph 18 of the Final Office Action, the Examiner has rejected claims 2-6, 20-40, 42-47, 57, 58, 61, 62, and 65 under the judicially created doctrine of obvious type double patenting as "being unpatentable over claims 1-53 of U.S. Patent No. 6,919,307." In particular, the Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '307 patent anticipate the instant claims." Furthermore, the Examiner has indicated in the Advisory Action of October 20, 2005 that

had Applicants' proposed response [to the Final Office Action] been entered, *claims 2-6, and 62-65 would no longer be included in the rejection*, and claims 41, 48 and 51-56 would have to be included in the list of rejected claims due to the proposed changes to the claimed structural formulas.

Without acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting examination, Applicants have cancelled claims 20-56 and 58-61 and have amended claim 57. Accordingly, the aforementioned rejection of the claims has been rendered moot and

Application No.: 10/001945

Docket No.: PPI-106CP2

the Examiner is respectfully requested to reconsider and withdraw this rejection.

Provisional Rejection of Claims 2-6, 20-40, 42-47, 57-59, 61-63, and 65 Under the Doctrine of Obviousness-Type Double Patenting

At paragraph 20 of the Final Office Action, the Examiner has provisionally rejected claims 2-6, 20-40, 42-47, 57-59, 61-63, and 65 under the judicially created doctrine of obviousness-type double patenting as "being unpatentable over claims 74-132 of co-pending Application No.10/962,333." The Examiner is of the opinion that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '333 application anticipate the instant claims."

Applicants respectfully submit that, while in no way admitting that the present claims are obvious over claims 74-132 of co-pending Application No. 10/962,333, upon allowance of the present application, Applicants will consider amending the claims of the '333 application, if appropriate, which will obviate the rejection.

Rejection of Claims 2-6, 57 and 62-65 Under 35 U.S.C. § 102(e)

At paragraphs 23 and 24 of the Final Office Action, the Examiner has maintained the rejection of claims 2-6, 57 and 62-65 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,548,477 and U.S. Patent Publication No. 2002/0193298. Specifically, the Examiner asserts that

Applicants point to amendments made to the definitions of variables R_3 and R_4 in claim 1 as establishing a patentable difference over the two references. The Examiner agrees. However, it should be noted that the amendments made to claim 1 are not reflected in dependent claims 2-6...and no such amendments were made to claims 57 or 62.

Applicants submit that the aforementioned rejection of the claims has been rendered moot in view of the amendments to the claims presented herein. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 2-6, 57, and 62-65 under 35 U.S.C §102(e).

Application No.: 10/001945

Docket No.: PPI-106CP2

Rejection of Claims 62 and 63 under 35 U.S.C. § 102(b)

At paragraph 25 of the Final Office Action, the Examiner has rejected claims 62 and 63 under 35 U.S.C. § 102(b) as being anticipated by Folkman *et al.* (U.S. Patent No. 6,017,954) [hereinafter "the '954 patent"]. The Examiner indicates that the '954 patent "teaches a compound in Example 28 which is used to treat angiogenic diseases" and that

[t]he compound of Example 28 corresponds to Applicants' compound of Formula I in which A is fumagillol; W is O; R₁, R₃, and R₄ are hydrogen, either X is methylene, n = 1, Z is methylene, P is N(R₆)R₇, and R₆ and R₇ are methyl, or n = 0, Z is ethylene, P is N(R₆)R₇, and R₆ and R₇ are methyl.

The Examiner further asserts that

[c]laims 1, 7, and 8 are no longer rejected over Folkman *et al.* (U.S. Patent 6,017,954) in view of Applicants' amendment to claim 1 deleting "hydrogen" from the definition of R₃ and R₄. Claims 62-64 continue to be rejected over Folkman *et al.* as the primary reference, albeit on slightly different grounds than in the first Office action. Note that Applicants have not limited the definition of R₃ and R₄ in claim 62, have broadened the definition of Z at line 15, and permit P to be other than hydrogen or a peptide at line 17.

Applicants respectfully traverse this rejection. For a prior art reference to anticipate a claimed invention in terms of 35 U.S.C. § 102, the prior art reference must teach *each and every element* of the claimed invention. Lewmar Marine v. Bariant, 827 F.2nd 744, 3 USPQ2nd 1766 (Fed. Cir. 1987).

Applicants respectfully submit that claims 62 and 63 have been amended to mirror the amendments made to claims 1, 7 and 8 in the Response to the First Office Action, filed on June 20, 2005. Accordingly, claims 62 and 63, as amended, are directed to compounds in which R₃ and R₄ are each, independently, substituted alkyl, substituted aryl or substituted or unsubstituted heteroaryl; or R₃ and R₄, together with the carbon atom to which they are attached, form a carbocyclic or heterocyclic group; or R₃ and R₄ together form an alkylene group. In addition, claims 62 and 63, as amended, are directed to compounds in which P is hydrogen or a peptide consisting of from 1 to about 100 amino acid residues attached at its carboxy terminus to Z. The '954 patent does not teach or suggest such compounds. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection of the claims.

Application No.: 10/001945

Docket No.: PPI-106CP2

Rejection of Claim 64 under 35 U.S.C. § 103(a)

At paragraph 26 of the Final Office Action, the Examiner has rejected claim 64 under 35 U.S.C. §103(a) as being obvious over Folkman *et al.* (U.S. Patent No. 6,017,954) as applied against claims 62 and 63, and further in view of Yanai *et al.* (U.S. Patent No. 5,422,363) [hereinafter "the '393 patent"] or Folkman *et al.* (U.S. Patent No. 6,086, 865) [hereinafter "the '865 patent"]. The Examiner indicates that the '954 patent teaches that the compounds can be administered to treat angiogenic diseases, but does not specifically teach the treatment of rheumatoid arthritis. Further, the Examiner indicates that the '363 patent and the '865 patent teach the administration of fumagillol derivatives to treat diseases associated with angiogenesis, such as rheumatoid arthritis. Specifically, the Examiner states that

[i]t would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the compounds of Folkman *et al.* '954 so as to treat rheumatoid arthritis, because the compounds of Folkman *et al.* '954 are disclosed to be useful in treating angiogenic diseases in general, and because Yanai *et al.* and Folkman *et al.* '865 teach that rheumatoid arthritis is an angiogenic disease treatable by similar fumagillol derivatives.

Applicants respectfully traverse this rejection for the following reasons. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd. 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Application No.: 10/001945

Docket No.: PPI-106CP2

As discussed in more detail above, the '954 patent fails to teach or suggest the claimed compounds or methods of using the same. Moreover, the secondary references relied upon by the Examiner, namely, the '363 patent and the '865 patent, do not make up for the deficiencies of the primary reference in that they also fail to teach or suggest the claimed compounds, or methods of using the same. In view of the foregoing, Applicants respectfully submit that the '954, the '363 and the '865 patents, alone or in combination, fail to render the claimed invention obvious. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection of the claims.

CONCLUSION

In view of the above amendments and remarks, Applicants believe that the pending application is in condition for allowance.

Applicants believe that no fee is due with this Amendment and Response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. PPI-106CP2 from which the undersigned is authorized to draw.

Dated: November 29, 2005

Respectfully submitted,

By 

Maria Laccotripe Zacharakis, Ph.D., J.D.

Registration No.: 56,266

LAHIVE & COCKFIELD, LLP

28 State Street

Boston, Massachusetts 02109

(617) 227-7400

(617) 742-4214 (Fax)

Attorney/Agent For Applicant